REMARKS

The Office Action mailed June 16, 2003 has been received and reviewed. Claims 1 through 15 are currently pending in the application. Claims 1 through 15 stand rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Maintenance Fee

The application was rejected due to an alleged failure to pay the maintenance fee. Applicants traverse the rejection and submit herewith documents as evidence of payment for the four year maintenance fee for U.S. Patent 5,885,966. Documents submitted include: Copy of Return Receipt Post Card (date stamped), Maintenance Fee Statement, Copy of Fee Payment Check #2956, Maintenance Fee Transmittal Form, and Fee Address Indication Form. Applicants request that the Examiner consider all the submitted documents as proof of payment so that reissue procedures may proceed for this patent.

37 CFR 1.172(a) Ownership not established

The reissue application was rejected for an alleged failure to meet the requirements of Rule 172(a). Submitted herewith are corrected documents of Assent of Assignee, chain of title, copy of assignments, etc. In view of the foregoing, applicants request that the reissue application proceed.

Offer to Surrender Patent

Applicants submit herewith a corrected Offer to Surrender Patent reflecting the correct ownership of the patent. In view of the foregoing, applicants request that the reissue application proceed.

Oath/Declaration

Claims 1-15 are rejected as based upon a defective reissue declaration under 35 U.S.C. 251. Applicants respectfully request that this rejection be withdrawn.

Applicants have submitted a corrected supplemental reissue declaration identifying the correct reissue application serial number and filing date of the patent for which reissue is being requested. Particularly, Applicants now correctly request reissue of U.S. Patent 5,885,966, an application for which was filed on December 5, 1997 and assigned application serial number 08/981,557.

Applicants have also correctly stated that reissue is being requested for a patent that was filed under 35 U.S.C. 371. Namely, Applicants now correctly claim priority under 35 U.S.C. 371 from PCT International Application Number PCT/NL96/00223, filed on 6 June 1996, which itself claims priority from U.S. Patent application serial nos. 08/477,298 and 08/476,013 both filed on 7 June 1995.

Specification

As applicants have amended the specification per the Examiner's suggestions to correct minor typographical and clerical errors, applicants believe the objection to be overcome.

35 U.S.C. 112 second paragraph

Claims 9-15 are rejected under 35 U.S.C. 112, second paragraph. Applicants have amended the claims, and, in view of the amendments, respectfully traverse this rejection.

Applicants have amended claims 9, 11, and 13 to overcome the rejections, and applicants respectfully request that the rejection of claims 9-15 be withdrawn.

Claim Objections

Applicants have corrected the informalities regarding the text of claims 3, 9 and 14. Specifically, in claim 3, line one "Peptides" was changed to "Peptide." At claim 9, line 1, "claims" was changed to "claim." Lastly, at claim 14, lime 1, "effect" was changed to "affect."

Improper Dependent Form

Applicants have amended claim 5 to be properly dependent as requested by the Examiner. Claim 5 was amended to include the element: "wherein a cysteine is placed before the glutamic acid at position 1 in LHRH."

Double-Patenting Rejection Based on U.S. Patent 6,284,733.

Claims 1-4 and 6-15 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of the U.S. Patent 6,284,733. To avoid further expense and time delay, applicants elect to expedite prosecution of the present application by filing a terminal disclaimer to obviate the double patenting rejections in compliance with 37 CFR §1.321(b) and (c). Applicants' filing of the terminal disclaimer should not be construed as acquiescence of the double patenting of obviousness-type double patenting rejections. Enclosed is the terminal disclaimer and fee.

35 U.S.C. § 102(b) Anticipation Rejection

Anticipation Rejection Based on GB Patent No. 2,228,262.

Claims 1, 9, 11, 12, and 14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the GB Patent 2,228,262. Applicants respectfully traverse this rejection.

Applicants have amended independent claim 1 to include the limitation: "position 6 of at least one of the constituting LHRH decapeptides is replaced by a dextrorotatory amino acid with a side chain that can be coupled to a carrier compound wherein said contiguous decapeptides are joined with a terminus to terminus linkage." The GB patent does not teach the terminus to terminus linkage of the contiguous LHRH decapeptides of claim 1. The '262 Patent discloses a GnRH dimer that is formed by linkages between D-Lys^6 amino acid side chains located centrally within the GnRH peptide. The contiguous, terminus to terminus linked, tandem peptides of claim 1 of the current invention are clearly distinguishable and can not be construed to be the GnRH conjugates of the '262 patent. Therefore, the limitation in independent claim 1 is not anticipated by the GB Patent '262 and the applicants respectfully request that the rejection of claim 1 be

withdrawn. Applicants further submit that claims 9, 11, 12, and 14 are allowable as being dependent from novel independent claim 1.

35 U.S.C. § 103(a) Obviousness Rejections

Obviousness Rejection Based on GB Patent 2,228,262.

Claims 10 and 13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over GB Patent 2,228,262. Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness has not been presented. To establish a *prima facie* case the prior art must provide some motivation to combine the references and there must be a reasonable expectation of success (MPEP §§ 2143, 2143.01 and 2143.02). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d (BNA) 1529, 1531 (Fed. Cir. 1988). The Office has not established a motivation to combine the references or addressed the expectation of success.

G.B. Patent '262 does not motivate, teach, or suggest the use of a contiguous peptide with terminus to terminus linkage as is described in claim 1. The Examiner points out that the '262 patent suggest the use of a dimer conjugate with an oil-in-water emulsion. In particular, the GB Patent '262 discloses: "in the present invention . . . the GnRH peptide analogue is conjugated to either an immunogenic carrier substance or to another molecule of the GnRH peptide analogue of *through an amino acid located centrally within the peptide chain* of the analogue" (see GB Patent, page 5, lines 19-25). (Emphasis added). The Patent '262 continues, "the conjugate may be accompanied by a suitable adjuvant" (see GB Patent, page 7, lines 9-10). While this may suggest the combination of the dimer conjugate of the GB Patent '262 with an oil-in-water emulsion, the applicants maintain this does not teach or suggest the use of the contiguous terminus to terminus tandem peptide of the current invention in combination with a water-in-oil emulsion.

In fact, the applicants affirm that '262 patent teaches away, and is motivation not to use of the terminus to terminus linked tandem peptide. The GB Patent '262 claims that its GnRH dimer conjugate is different from other GnRH analogues and that its unique conjugation site at a center amino acid make it more desirable than other embodiments (see, GB Patent, page 5, lines 17-25).

This teaches away from the limitation, as described in claim 1, of a tandem LHRH peptide with a terminus to terminus linkage. Therefore, one of ordinary skill in the art would find no motivation to use a tandem GnRH with terminus to terminus linkage.

Moreover, there is no evidence of a reasonable expectation of success (MPEP § 2143.02). The GB Patent '262 discloses that its GnRH dimer conjugate is unusual and its unique centrally located linkage site at an internal amino acid is more immunogenic than other embodiments. Therefore, one of ordinary skill in the art would not expect a tandem LHRH with a terminus to terminus linkage to be a successful immunogen (see, GB Patent '262, page 5, lines 17-25).

Absent a showing of motivation or reasonable expectation of success, the Office has failed to provide a *prima facie* case for obvious pursuant to 35 U.S.C. § 103 and the applicants request that the rejection of claim 1 be withdrawn. Applicants further submit that dependant claims 10 and 13 are allowable as being dependent on nonobvious independent claim 1.

Obviousness Rejection Based on U.S. Patent 5,723,129 to Potter et al in view of the GB patent 2,228,262 or the GB Patent 2,196,969.

Claims 1 and 6-15 are rejected under 35 U.S.C. 103(a) as being obvious over Potter et al. (U.S. Patent 5,723,129) in view of GB 2,228,262 or GB 2,196,969. Applicants respectfully traverse this rejection.

M.P.E.P. 706.02(j) sets forth the standard for a section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or reference when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be in the prior art, and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (Emphasis added).

The 35 U.S.C. § 103(a) obviousness rejections of claims 1 and 6-15 are improper because the references relied upon by the Examiner fail to teach or suggest all of the limitations of the presently claimed invention. Claims 6-15 ultimately depend on independent claim 1.

Potter *et al.* discloses chimeric proteins comprising a leukotoxin fused to GnRH multimers. The Office admits that Potter *et al.* does not teach GnRH multimers with D-Lysine at residue 6. However, the GB Patent '262 and the GB patent '969 are alleged to disclose GnRH analogs in which residue 6 is D-Lysine. The Examiner has suggested that it would have been obvious to one of ordinary skill in the art to combine these references to generate the claims of the current invention.

Applicants assert that the claims are not obvious over Potter *et al.* in view of the GB Patents. Potter *et al.* teaches a GnRH multimer fused to a leukotoxin. The combination of the GB Patents '262 and '969 teach a dimer of [D-Lys^6]GnRH attached to one another through the D-Lys^6 side chains. The suggested combination fails to teach or suggest all the limitations of claim 1 of the current invention: "*at least two contiguous LHRH decapeptide sequences wherein the amino acid glycine at position 6 of at least one of the constituting LHRH decapeptides is replaced by a dextrorotatory amino acid with a side chain that can be coupled to a carrier compound wherein said contiguous decapeptides are joined with a terminus to terminus linkage.*"

These differences are significant and the combination of references would not have been obvious to one skilled in the art at the time of the invention. Particularly, Potter *et al.* teaches a leukotoxin fused to a GnRH multimer and that the leukotoxin is advantageous in creating a sufficiently immunogenic protein. Potter *et al.* teaches away from using simple GnRH tandem peptide, as described in the limitations of claim 1, as a vaccine candidate. Potter *et al.* teaches that a fusion protein including the leukotoxin presents T-cell epitopes thereby eliciting a robust T-cell dependant immune response. Furthermore, Potter *et al.* teaches that the T-cell recruitment is essential in generating an immune response to the endogenous GnRH protein (See Potter *et al.*, column 3, lines 12-20). Given the teaching of Potter *et al.* that the leukotoxin is essential to proper immunogenicity, it would not be obvious to form a simple tandem GnRH peptide with no leukotoxin as is described in claim 1. Thus, the combination of Potter *et al.* and GB Patents '262 and '969 fail to teach or suggest all the limitations of the presently claimed invention as set forth in claim 1.

Therefore, the applicants assert that the Office has not established that "it would have been obvious to one of ordinary skill in the art . . . to form the chimeric proteins of Potter *et al.* in which the amino acids corresponding to residue 6 of GnRH are D-amino acids such as D-Lysine" (page 8 of the communication). To the contrary, one of ordinary skill in the art would have thought it essential to use a leukotoxin GnRH fusion protein and would have expected a failure of the presently claimed invention.

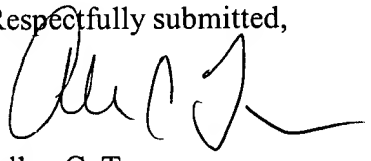
Thus, independent claim 1 should be allowable over Potter *et al.* and the GB Patents '262 and '969, taken either individually or in combination, and respectfully requests reconsideration and allowance thereof.

Applicants further submit that claims 6-15 are allowable as being dependant from an allowable nonobvious independent claim1.

CONCLUSION

Claims 1 through 15 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, it is respectfully invited to contact applicants' undersigned attorney.

Respectfully submitted,



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